

### **REMARKS**

The claims are not amended with this paper. Currently pending in the application are claims 11, 16-20, and 22-35.

#### **Rejections Under 35 U.S.C. § 103**

(i) In a previous Office Action (dated November 2, 2007), claims 11, 16-20, 22-26 and 33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Saito et al., in view of Goodman and Gilman, in view of Elkhoury et al. and further view of Ptchelintsev et al. Applicants respectfully disagree and traverse this rejection. Although the present Office Action presents a “modified” rejection under 35 U.S.C. § 103(a) (see below), the Office Action also states that “the prior rejections under 35 USC 103 are maintained.” Applicants therefore address the prior rejections and provide the following remarks

The present invention is directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

Saito purportedly teaches the synergistic effects of morphine and lidocaine or bupivacaine when systemically administered via bolus injection or continuous coinfusion. Saito does not teach the administration of butamben. Similarly, Saito does not teach the topical administration of these compounds nor does Saito suggest that the synergistic effect would be retained in the periphery via topical administration. Saito does not and cannot render obvious the claimed subject matter by itself, and the prior Office Action does not allege that Saito alone renders the claimed subject matter unpatentable.

Despite the statements made in the prior Office Action, none of the remaining cited references can cure the deficiencies of the Saito reference. The prior Office Action cites the Goodman reference as teaching that some local anesthetics have common activities, and that benzocaine and butamben can be applied topically. In any event, the prior Office Action does not suggest that Goodman teaches that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. The prior Office Action points to nothing in Goodman that could teach

or suggest that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

According to the prior Office Action, Elkhoury teaches “the topical application of opioid analgesic drugs such as morphine . . . to produce an analgesic effect in a localized area.” The prior Office Action further stated that Elkhoury teaches that “peripheral analgesia of morphine was known.” However, as noted previously, the prior Office Action does not suggest that Elkhoury teaches or suggests the use of butamben together with morphine. Applicants further point out that Elkhoury lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

The prior Office Action relied on Ptchelintsev as teaching that butamben is a topical analgesic. The prior Office Action does not allege that Ptchelintsev teaches or suggests the use of morphine. Applicants further point out that Ptchelintsev lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

Although the current Office Action appears to take the position that synergism in the periphery would be expected based on synergism for systemically administered drugs (see, e.g., Office Action at page 5), Applicants disagree. Even if synergism for systemically administered drugs were known, synergism for topically administered drugs was not known at the time the invention was made, and would not have been predictable. When acting centrally, drugs can have many possible locations to act; however, in the periphery, it is necessary for two drugs to act on the same axon to have a synergistic effect. That two topically-administered drugs could act synergistically would not have been expected at the time the invention was made.

The present Office Action further states that the Kolesnikov et al. journal article (Anesth. Anal. (2003), volume 97, pp. 1103-1107) concludes that “the synergistic effects of topical lidocaine and morphine were not unexpected.” Applicants disagree. It will be appreciated that the cited Kolesnikov et al. article was published in 2003, well after the effective filing date of the present application (which claims priority to a provisional application filed in April, 2000 and a utility application filed in April, 2001). A journal article published in 2003 is not prior art and does not provide any evidence that

the claimed subject matter would have been obvious to one of ordinary skill in the art at the time the priority application(s) were filed, nor at the time the presently-claimed invention was made.

Additionally, Applicants disagree with the statement in the present Office Action that “synergy was expected due to the many references (presented by applicant as prior art) including Saito et al. . . . [t]hus though synergy has been demonstrated by the applicants, it is not an unexpected result.” Office Action at pages 6-7. As noted above, even if Saito discloses synergy of certain compounds administered systemically, there would be no reasonable expectation that synergy would exist when compounds are administered peripherally. That two topically-administered drugs could act synergistically would not have been expected at the time the invention was made.

From the foregoing it can be seen that none of the cited references, whether taken alone or in any combination, teaches or suggest the combination of features of the presently-claimed subject matter, in which a method of providing topical analgesia to a subject includes topically administering to peripheral sites in the subject a pharmaceutical composition comprising (i) synergistically effective amounts of morphine and butamben and (ii) a physiologically acceptable topical excipient, to potentiate analgesia at the peripheral sites.

It is respectfully submitted that the topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected to one of skill in the art of pain management at the time the present invention was made. Prior to the teachings of the instant application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

In fact (as detailed at length in the Response filed August 16, 2007, which is incorporated herein by reference), several medical reports published before the filing of the present application teach that methods comprising the topical use of morphine fail to stimulate peripheral sites. As described previously, the Raja *et al.* (Anesthesiology 77:1143-7; 1992), Rosenstock *et al.* (Ref. Anesth. 21:93-8; 1996), Picard *et al.* (Pain 72:309-18; 1997), and Yarussi *et al.*, (Reg. Anesth. Pain. Med. 24:142-5; 1999) references described various studies in which peripheral analgesia was not seen with morphine.

Further, the Declaration of Sandra C. Roerig, Ph.D., submitted in related application No. 09/975,812 (now U.S. Patent No. 6,790,855) and discussed in the Response filed August 16, 2007, provided evidence that, prior to the invention of the claimed subject matter, scientists did not expect that morphine and lidocaine would synergistically potentiate the antinociceptive effects of each other in the periphery. The Office Action does not discuss this Declaration other than to say that it is “not persuasive.” However, Applicants respectfully submit that the Declaration provides clear evidence that the claimed subject matter was not obvious at the time the invention was made.

For at least the foregoing reasons, there would be no motivation to combine Saito and/or Goodman with Elkhoury and Ptchelintsev. As discussed above, Elkhoury and Ptchelintsev describe the topical administration of morphine and butamben, respectively. Although the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there would have been no expectation of their synergistic effect in the periphery. Saito does not rectify this deficiency; the synergistic effect described systemically by Saito would not be anticipated when administered topically as discussed above. As noted above, the Office Action’s mention of references demonstrating synergy between compounds apparently does not refer to references showing synergy at a peripheral site when administered topically.

In the prior Office Action, the Examiner also stated that combining “two compositions . . . useful for the same purpose, in order to form a third composition to be used for the very same purpose” is *prima facie* obvious. Even if that were true, a synergistically effective composition would not be *prima facie* obvious. Saito does not

rectify this deficiency, for at least the reason that any synergism of Saito in systemic administration would not be expected when administered topically to peripheral sites, as discussed above.

Applicants respectfully contend that the Office Action does not even make out a *prima facie* case of obviousness of the present claims. Reconsideration and withdrawal of the rejection is proper and the same is requested.

In the prior Office Action, claims 27-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Saito, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Mayer et al. Claims 34-35 were rejected under 35 U.S.C. § 103 as being unpatentable over Saito, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Soo et al. Again, Applicants disagree.

As stated above, the pending claims are directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

As discussed in detail above, claims 11-13, 16-26, and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either Mayer or Soo with the combination of Saito, Goodman, Elkhoury and Ptchelintsev fails to remedy the deficiencies of those references as described above. The additional references, whether taken alone or in any combination, cannot render obvious any of the pending claims.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

(ii) In the present Office Action, claims 11, 16-20, 22-26 and 33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury et al., U.S. Patent No. 5,589,480, in view of Elden, U.S. Patent No. 5,814,659, and further in view of Saito et al. (Anesthesiology, Vol. 89(6) and Goodman and Gilman. Applicants respectfully disagree and traverse this rejection.

The teachings of Elkhoury are discussed above. As noted above, and as the Office Action concedes, Elkhoury does not teach or suggest the use of butamben together with morphine. Applicants further point out that Elkhoury lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. Elkhoury cannot render obvious the presently-pending claims.

Elden (U.S. Patent No. 5,814,659) cannot remedy the deficiencies of Elkhoury. The present Office Action states that Elden teaches topical analgesic compositions and methods for inducing topical analgesia, and topical compositions including butamben. However, Elden does not teach or suggest the use of butamben together with morphine. Applicants further point out that Elden lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. Even if the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there is no expectation of their synergistic effect in the periphery. The Office Action states that combining “two compositions . . . useful for the same purpose, in order to form a third composition to be used for the very same purpose” is *prima facie* obvious. Even if that were true, a synergistically effective composition would not be *prima facie* obvious. Elden, alone or in combination with Elkhoury, cannot render obvious the presently-pending claims.

The teachings of Saito are discussed above. Saito purportedly teaches the synergistic effects of morphine and lidocaine or bupivacaine when systemically administered via bolus injection or continuous coinfusion. Saito does not teach the administration of butamben. Similarly, Saito does not teach the topical administration of these compounds nor does Saito suggest that the synergistic effect would be retained in the periphery via topical administration. Saito does not and cannot render obvious the claimed subject matter by itself, and the Office Action does not allege that Saito alone renders the claimed subject matter unpatentable. Moreover, Saito does not remedy the deficiencies of Elkhoury and Elden as discussed above.

The teachings of Goodman and Gilman are discussed above. The Office Action does not suggest that Goodman teaches that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. The Office Action points to nothing in Goodman that could teach or suggest that a synergistically effective

amount of morphine and butamben can be administered to a peripheral site. Moreover, Goodman and Gilman does not remedy the deficiencies of Elkhoury, Elden and/or Saito as discussed above.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

In the prior Office Action, claims 27-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Elkhoury in view of Elden, and further in view of Saito and Goodman, as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Mayer et al. Claims 34-35 were rejected under 35 U.S.C. § 103 as being unpatentable over Elkhoury in view of Elden, and further in view of Saito and Goodman as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Soo et al. Again, Applicants disagree.

As stated above, the pending claims are directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

As discussed in detail above, claims 11, 16-20, 22-26 and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either Mayer or Soo with the combination of Elkhoury, Elden, Saito and/or Goodman fails to remedy the deficiencies of those references as described above. The additional references, whether taken alone or in any combination, cannot render obvious any of the pending claims.

Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 is respectfully requested.

#### Supplemental Information Disclosure Statement

The Examiner's attention is directed to the Supplemental Information Disclosure Statement (IDS) filed with this paper. Applicants request that the Examiner consider

the references cited and return an initialed copy of the IDS to Applicants with the next Office Action or Notice of Allowance.

CONCLUSION

Applicants believe the pending application is in condition for allowance. Early and favorable action is earnestly requested.

Applicants conditionally petition for any extension of time necessary for consideration of this response. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 62069DIV2 (51590).

Respectfully submitted,

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